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EFFECTS OF DUSTS, GASES, VAPOURS, FUMES AND SMOKING ON GAS DIFFUSION - A CASE CONTROL STUDY

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Abstract: Airborne dusts are of particular concern because they are well known to be associated with classical widespread occupational lung diseases such as the pneumoconiosis, chronic obstructive pulmonary disease, occupational asthma etc. To examine the effects of dusts, noxious gases / vapours, fumes and tobacco smoking on the level and rate of change of the diffusing capacity of the lung for carbon monoxide (DLCO). In this paper I briefly review the significance of the single breath test of diffusing capacity for carbon monoxide (DLCO). **Methods:** A cohort study of 420 workers out of which 60 represented the control group. The examination was carried out as follows: Using modified MRC questionnaire (MRCQ) on respiratory symptoms, Anthropometric measurements, Clinical check up, Laboratory tests, Pulmonary function examination, Forced expirogram Spirometry (FEV_1,FVC, Tiffeneau Index), Single breathe method of diffusing capacity (DLCO). Qualitative exposure indicators were developed based on both, lifetime work and exposure histories. **Results:** DLCO measurements were done on 420 Workers engaged staff , COPD differential findings was tried to be obtained by using indirect parameters witch was at the level of significance FEV_1 (p<0,0001), Tiffeneau Index (100 x FEV1/FVC) at the level (p<0,001), the results for FEV_1 was related to the working environment conditions, whereas in relation to the category smoker with exception of a worker smoker at the mine Hajvalia (p<0.05), Tiffeneau Index (100 x FEV1/FVC) there were significant differences for the Tiffeneau Index for Leposavić and Magura (p<0.05) to the other groups of exposed workers we did not obtained statistically significant differences (p>0.05). The average rate of decline in DLCO (Mean for Nonsmokers/smokers): Coal seam surface Power Plant (n.s.21.8/s.21.0), Gasification (n.s.20.8/s.21.4), Procesing Lead and Zinc (n.s.18.9/s.18.3), Magnesite Mine (n.s.18.8/s.20.0), Cave exploitation (n.s.19.1/s.17.4), Lead and Zinc smelter (n.s.26.7/s.19.9), and Control group (n.s.25.7/s. 22.7).Compared with no-smokers, current smokers and ex-smokers had lower DLCO at baseline, but smoking status did affect in this control case study the change in DLCO only in two cases. **Conclusions:** Our results confirm a continuous deleterious effect of dusts, gases, vapours, fumes and tobacco smoking (DGVF) on DLCO, especially on exposed workers. Smoking was associated with lower DLCO levels, and was a significant predictor of rate of change in DLCO. Smoking status did affect the relationships between DGVF exposure and the level or rate of change of DLCO in this workers. Control methods should be implemented to prevent workers' exposures, and smoking cessation should be promoted.

KEY WORDS: DLCO,COPD, workers, dusts, gases, vapours, fumes and tobacco smoking

INTRODUCTION

Airborne contaminants occur in the gaseous form (gases and vapours) or as aerosols. Aerosols may exist in the form of airborne dusts, sprays, mists, smokes and fumes. In the occupational setting, all these forms may be important because they relate to a wide range of occupational diseases.

Chronic obstructive pulmonary disease (COPD) is a leading cause of death, particularly in developing countries (1), and is characterized by abnormal inflammatory response of the lungs to noxious particles and gases. Although smoking is the most important risk factor, other factors, including occupational exposure, may play a role in the etiology of COPD (2).

Altogether these findings suggest that the FEV_1 decline associated with occupational exposure is likely caused by airway disease. However, the possibility of occupational irritants being a risk factor of emphysema has not previously been explored. Silica and coal exposure was formerly linked with emphysema in experimental studies and workforce cohorts of miners, including autopsy studies (3). Lifetime occupational exposure occurring during the jobs most commonly done by COPD patients includes inhalation of mineral and biological dusts and gases / fumes, but the likelihood of these groups of agents producing emphysema has not been analysed.

In this study, exposure to gases or fumes was significantly associated with chronic bronchitis, and exposure to mineral dust and gases / fumes was associated with a higher symptom score in the quality

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of life questionnaire. Occupational exposure in our case control study was not strongly associated with any spirometry variable, but a consistent association was found between exposure to vapours and gas or fumes and better diffusion capacity.

Exposure to vapours, gases and fumes was associated with chronic bronchitis. A large body of evidence from previous population-based and workforce-based studies supports the notion that occupational exposure increases the risk of developing bronchitis (4-5). Experimental models have demonstrated that several inhaled agents, such as sulphur dioxide, vanadium, and endotoxin can induce chronic obstructive bronchitis (6-7).

The single-breath carbon monoxide diffusing capacity (DLCO) test is clinically useful in diagnosing pulmonary vascular and interstitial lung diseases and in detecting emphysema. The measurement of DLCO is determined by the diffusing capacity of the alveolar-capillary membrane and the volume of blood in the alveolar capillaries, the former being predominantly affected by diffuse interstitial pulmonary fibrosis (as seen in asbestosis) (8-9). The DLCO measurement is not substantially influenced by airway calibre. It is therefore an easy, non-invasive means of examining the integrity of the lung parenchyma in vivo and of monitoring the course of obstructive and restrictive lung diseases. Previous cross-sectional studies have shown that asbestos exposure reduces DLCO (10).

METHODOLOGY

The study was carried out at the Pathophysiology Institute of the Faculty of Medicine, University of Prishtina. The study recruited 420 participants divided in 7 groups. Out of the seven groups, six (6) groups with a total of 360 were exposed mining workers to: Lead and Zinc Smelter (60 participants), Pit Mine - Ajvalia (120 participants), Lead and Zinc Concentrate Processing - Leposavić (30 participants), Magnesite Mine - Magure (30 participants), Gasification (60 participants), Surface Coal Mine in Belaqevc, Obilić Power Plant (60 participants). The control group of workers (60 participants) included workers from the construction company GK from Prishtina, who practically were not exposed to the noxious elements to which miners at industrial plants of "Trepča" complex, Magure, open pit mine in Obilić (Belaqevc) and Obilić Power Plant were exposed.

Criteria for inclusion – Workers working at least for 5 years continuously in the workplaces within the abovementioned enterprises, or in cumulative manner for 10 years, at least in the period of last 20 years.

Criteria for exclusion – Workers who had any other pulmonary illness, and which could have repercussions on examined spirometry parameters.

All participants, including the control group were subjected to the following examina- tions:

Using modified MRC questionnaire (MRCQ) on respiratory symptoms

Examinations with modified MRC questionnaire for respiratory symptoms (Haxhiu, modified in 1976) will give a detailed review on respiratory problems.

Anthropometric measurements

Body height and weight was measured to each respondent by using a standard scale, whereas relative weight was calculated and expressed by Broca Index.

Clinical check up

Physician's check-up involved a detailed check-up of examined individual which encompassed general check-up, percussion, auscultation, blood pressure measurements, pulse etc. Findings were recorded at the questionnaire in the order indicated from the number 43 to number 73.

Laboratory tests

Laboratory tests consisted of finding red blood count, haemoglobin, leucocytes and sedimentation. Standardized laboratory methodology has been applied.

Application of MRC questionnaire

A detailed anamnesis was taken in advance from the participants according to the modified MRC questionnaire for respiratory (breathing) symptoms, which according to the order of study questions, without exception, paying attention not to exclude any of the important facts, it ensured us with accurate information as to what must be undertaken and what requires attention in the conducted research. The specific importance of the questionnaire stands on the fact that it provides very important information, which must be taken into account when deciding about diagnosis, whether a person suffers from bronchial asthma or obstructive chronic bronchitis. World Health Organization has set the criterion for this matter, and it has been included at the questions of the questionnaire numbered 11 and 23. Question no. 11 contains as follows: Have you coughed almost every day for three months and at least in the last two years? If participants answer is positive, then it can be considered that this person suffers from the chronic bronchitis. Question no. 23 helps us for the differential diagnosis within the obstructive syndrome of pulmonary insufficiency and mucus in order to determine whether we are dealing with patients facing bronchial asthma. The question is as follows: Have you experienced suffocating attacks associated with chest wheezing? If the answer is positive, then it is considered that it is possible that the patient suffers from bronchial asthma.

Spirometry determination - Dynamic spirometry is one of the first tests for measurement of lung volume. Testing of forced expiratory flow was measured by "Godart" pulmo-test spirometer. Spirometric measurements were made after the purpose methods and the purpose were clearly described to the participants. Forced expiration was analysed, where one of variables (volume or time) was fixed. In our case time was fixed at the x-axis, so that the obtained

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volume from the acquired curve is described as expiratory forced volume for a certain time, e.g. Forced expired volume in the first second (FEV_1). Measurements were carried in the standing or sitting position. The participants were wearing a nose clip, and slowly started to inspire starting from functional residual capacity (FRC) to the total pulmonary capacity (TPC) followed by a full and forced expiration to the residual volume (RV). Several measurements were conducted until we did not obtain two reproducible curves. Forced volume capacity (FVC) was calculated from the forced expiration volume curve. Forced expired volume in the first second FEV_1, 100x FEV_1 / FVC, and forced expiratory flow at 50% of FVC (FEF_{50}), forced expiratory flow between 25 and 75% of FVC (FEF_{25-75}), forced expiratory flow at 75% of FVC (FEF_{75}) [8].

Determination of acid-alkaline status and respiratory gases in capillary blood

The respiratory gas was done at a standstill form with arterial puncture, (previously hyper-immunized with butyl nicotine capsaicin) from which the parameters of the partial pressure of oxygen pO_2, partial pressure of carbon dioxide pCO_2, oxygen saturation of haemoglobin and acid base status of the blood, using analyser IL-213 few minutes after the samples were taken. Standard vials solutions pH, PaO_2 and $PaCO_2$ have been used as standards for verifying the measurement accuracy. The ointment residue was removed 10-15 minutes later. Every two heparinized tubes were filled with capillary pressure without squeezing them. Sample taking time is about two minutes.

RESULTS

Direct and indirect indicators of airways obstruction have been presented individually by the median value (X), standard deviation (SD) and standard error (SEM). By comparing obtained findings particular attention was paid to smoking habit. As to smoking habit, respondents are divided to:

- Non-smokers, the ones that never smoked, and
- Smokers, the group that presently smokes.

Determining the transfer factor for CO through Steady State method

In practice, the test is performed by having the test subject blow out all of the air that they can to reach residual volume. The person then takes a full vital capacity inhalation of a test gas mixture that contains a small amount of carbon monoxide (usually 0.3%) and some helium or other non-absorbed tracer gas. The test gas is held in the lung for about 10 seconds and then is exhaled from the lung. The first part of the expired gas is discarded and the next portion which represents gas from the alveoli is collected. By analysing the concentrations of carbon monoxide and helium in the inspired gas and in the exhaled gas, it is possible to calculate how much carbon monoxide was taken up during the breath hold, and the partial pressure of carbon monoxide was during the breath hold. This method is known as the single-breath diffusing capacity test. All patients were examined while seated after a period of about 10 minutes' rest. The Filley's method requires that the expired air and arterial blood should be collected simultaneously.

STATISTICAL DATA PROCESSING

Comparison of the groups of participants was analysed by ANOVA statistical method. Whilst the computer program INSTAT-3 and STATISTICA FOR WINDOWS was used for data processing.

	Age (years)			Body height (cm)			Body weight (kg)			Relative weight (Broca index)			Length of service(years)		
	Mean	SD	SEM	Mean	SD	SEM	Mean	SD	SEM	Mean	SD	SEM	Mean	SD	SEM
Obilić Surface coal seam/Power Plant	44.6	9.2	1.09	170	6.1	0.72	74.4	11.6	1.36	100.3	15.9	1.88	13.3	7.2	0.85
Obilić - Gasification	35.5	10.7	1.29	169.1	6.6	0.8	67.7	10.2	1.24	97.5	12	1.46	15.5	9.4	1.14
Leposavić Processing of concentrates	46.5	6.3	0.9	173.5	6.9	1	77	11.9	1.72	106.1	16.9	2.44	21.4	7.6	1.1
Magura-Magnesite Mine	45.1	5.9	1.15	173.3	5.9	1.15	73.2	9.5	1.86	100	11.9	2.32	19.9	8.5	1.67
Ajvalia – Cave exploatation	46.6	7	0.65	171.8	6.2	0.57	73.2	11.5	1.05	100.7	16.3	1.49	23.5	7.3	0.67
“Trepča” - Lead and zinc smelter	40.6	7.7	0.98	171.8	6.8	0.86	74.8	14.9	1.89	102	12.2	1.55	15.6	8.3	1.06
“Ramiz Sadiku” - Control group	39.8	8.5	1.31	170.5	5.8	0.66	71.6	9.1	1.03	101.9	14	1.59	14.2	11.9	1.35
One Way ANOVA	F=18.23, p<0.0001			F=4.193, p<0.001			F=2.362, p<0.05			F = 1.879, p>0.05			F = 19.414, p<0.001		

Table 1. Basic characteristics of participating workers

Table 2. Gives of subjects according to the smoking habits

Group of indu- strial workers	Non-smokers		Smokers		Total	
	N	%	N	%	N	%
Obilić Surface coal seam/Power Plant	34	56.9	26	43.1	60	100
Obilić -Gasification	24	39.7	36	60.3	60	100
Leposavić Processing of Lead & zinc concentrates	7	22.9	23	77.1	30	100
Magura-Magnesite Mine	12	38.5	18	61.5	30	100
Ajvalija – Cave exploitation	42	35.3	78	64.7	120	100
"Trepča" - Lead and zinc smelter	22	37.1	38	62.9	60	100
"Ramiz Sadiku" - Control group	26	43.6	34	56.4	60	100
X^2-test	X^2=16.23, p<0.05					

Table 2. The total number of participants and categories of subjects according to the smoking habits

Results of spirometry parameters for FVC (L) and FEV_1 (L) was at the level of statistical significance of (p<0.0001) for the workers participants in relation to their workplaces, while as to the category of smokers and non-smokers, with exception of a worker smoker at the mine Hajvalia (p<0.05), to the other groups of exposed workers we did not obtained statistically significant differences (p>0.05). Chart 1.

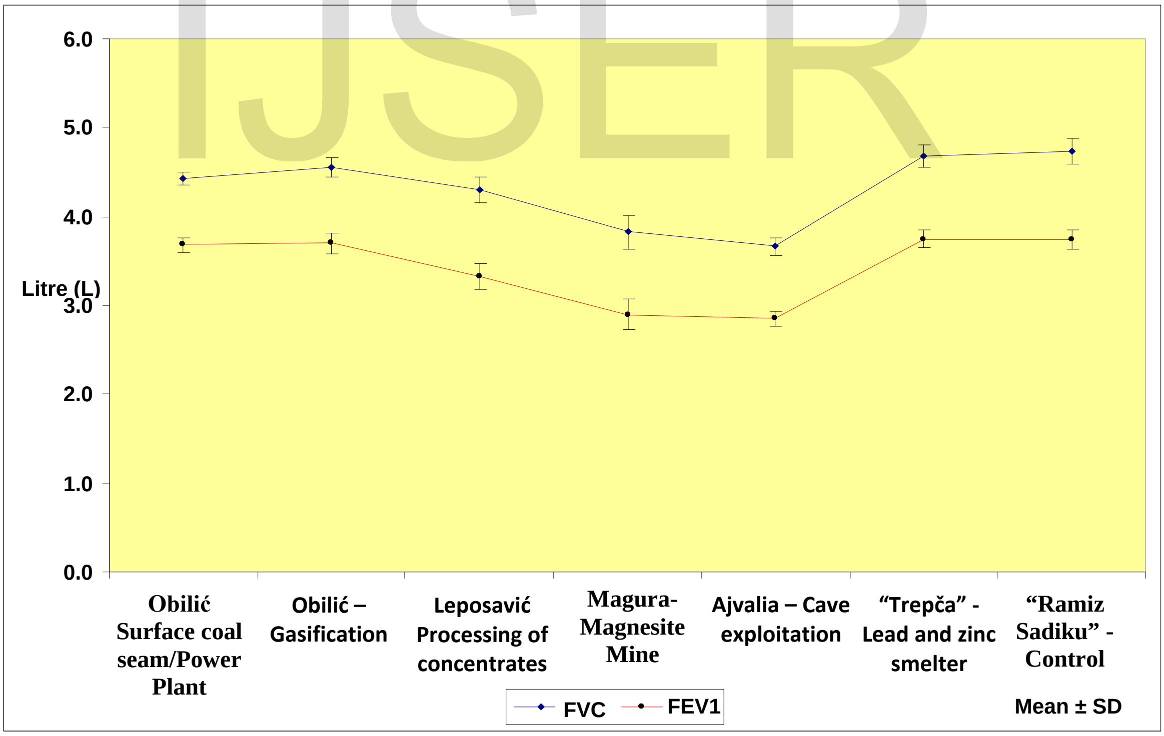

Chart 1. Lung function parameters for the examined working units at industrial pools in Kosovo

Values for Tiffneau Index in relation to workplaces were statistically significant at the level (p<0.001),for the category of workers smokers, there were significant differences for the Tiffeneau Index for Leposavić and Magura ($p<0.05$) while for all the other there were no significant differences ($p>0.05$). Chart2.

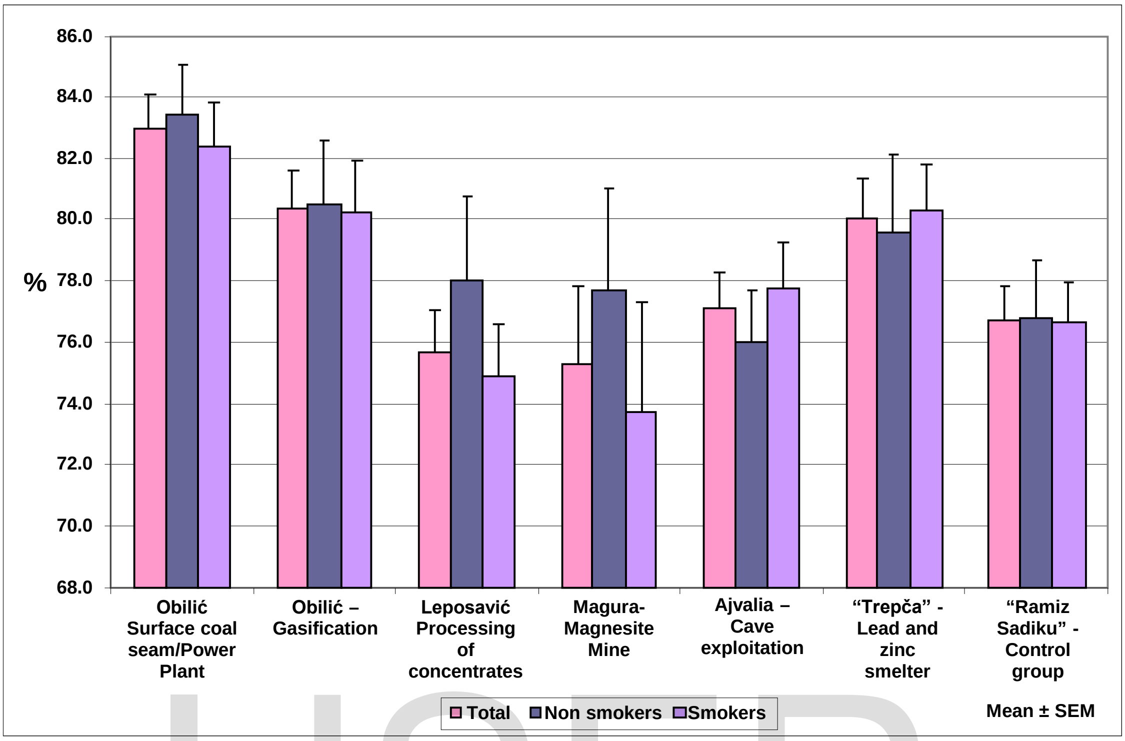

Chart 2. Tiffneau index in subjects in groups, as well as the categories of subjects smokers and non-smokers

The analysis of respiratory gases partial pressures in arterial blood has shown a difference between workers at concentrate processing in Leposavić (lead and zinc concentrate processing). Differences were found by analysis of variance (One Way ANOVA), along with statistical significance at the level ($p<0.001$).

As to the values for pH among certain groups, we didn't find significant differences ($p>0.05$). But, the values of partial pressure in capillary blood for PaO_2 and $PaCO_2$ to exposed workers and control group workers we got significant statistical differences ($p<0.001$). The chart 2. shows values for partial pressure in capillary blood (PaO_2) which was the lowest to workers in Leposavić 8.91 kPa (SD 6, 0), whereas the highest was to workers in control group RS 10.04 kPa (SD 5, 3). Partial pressure in capillary blood ($PaCO_2$) was the lowest to the workers in Leposavić 4.53 kPa (SD 2, 6), and the highest was to participants workers from the mine Hajvalija 5.01 kPa (SD 5, 4). Chart3.

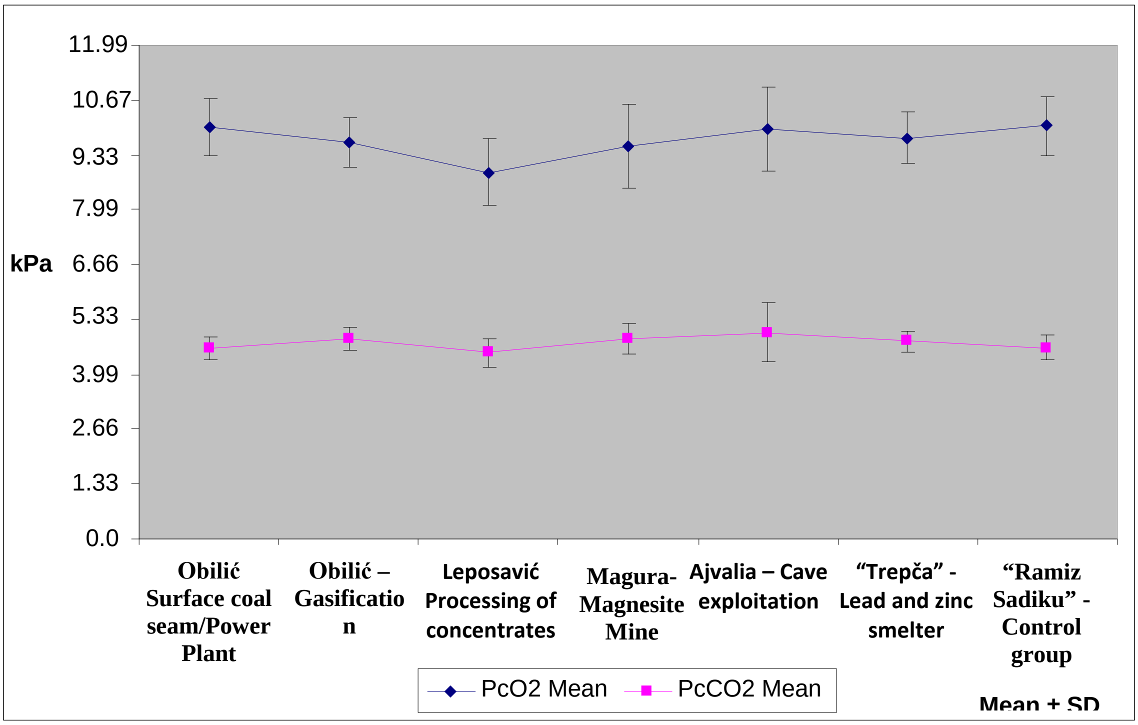

Chart 3. Partial pressures of respiratory gases

Comparing the obtained values of the transfer factor for CO for all groups of participants

With the analysis of the obtained values of DLCO in relation to specifics of workplaces, we gained significant differences in levels (p <0.0001), while the obtained values in DLCO related to categories of smokers / nonsmokers to all groups of workers did not have significant differences (p> 0.05), except for participating smoking workers who work in the lead and zinc smelter (TR), where the difference was in the level of (p <0.01), while in the control group (p <0.05). Here, significant changes were recorded primarily in connection with the specifics of the workplaces with two exceptions in the category of smokers. (Tab. 3, Table 4).

A group of workers	DLCO (r									
	Total			No						
	Mean	SD	SEM	Mean						
Obiliq Surface coal seam/Power Plant	21,5	5,0	0,59	21,8						
Obiliq - Gasification	21,2	5,1	0,62	20,8	4,2	0,81	21,4	5,7	0,88	p>0,05
LeposaviqProcess-ing of concentrates	18,4	6,6	0,95	18,9	8,9	2,69	18,3	5,9	0,97	p>0,05
Magura-Magnesite Mine	19,6	6,5	1,27	18,8	7,6	2,41	20,0	5,8	1,46	p>0,05
Hajvali – Cave exploitation	18,0	5,5	0,51	19,1	4,8	0,				
"Trepça" - Lead and zinc smelter	22,4	7,2	0,91	26,7	6,4	1,				
"Ramiz Sadiku" - Control group	24,0	6,7	0,76	25,7	6,1	1,				
One Way ANOVA	F = 12,48, p<0,001									

Table 3. DLCO (transfer factor) in group of workers, as well for the categories of smokers and non-smokers

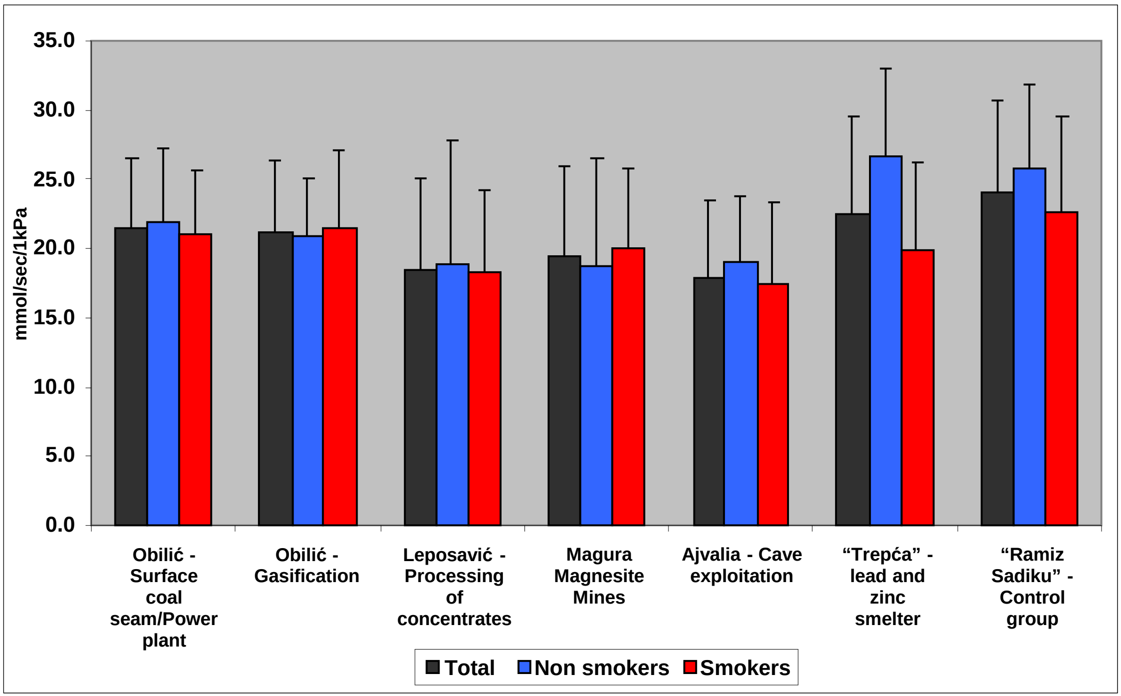

Chart 4. DLCO (transfer factor) in group of workers, as well for the categories of smokers and non-smokers (mmol.sec^{-1}kPa^{-1})

DISCUSSION

In June 2008 the Danish Working Environment Research Fund called for applications for reviews, in the form of reference documents, within the theme "Correlations between chronic bronchitis and various types of physical and chemical exposures at work" , or exposures to various types of gases, smoke, irritants or chemicals etc. at work, and the development of chronic bronchitis". Following the analysis of the results obtained from spirometric parameters, the differenced were at statistical significance limits and the differences were not great amongst all the examined groups, although considerable differences were noticed at the exposed groups at the results of general parameters compared to the control group, a group which in principle was not exposed to the same or similar pollutants at their working environment. Nevertheless, it can be concluded that irritation and induction of inflammation at the respiratory ways was significant and more severe at the workers exposed to pollutants generated at the departments where lead and zinc processing work has taken place. Following the analysis of responses provided by participants related to breathing symptomatology (cough, panting, coughing, chest wheezing), it was argued that the results of this study do not differ considerably from the data provided by literature (11).

The aim of the research was to establish possible correlation between participants exposed to air pollutants at work places, especially the categories of participants who are smokers and non-smokers, workers in industrial-mine pools and mines. Forced expiratory volume in first second (FEV1), relation between forced expiratory volume in first second and forced vital capacity (FEV1/FVC), the effect of aero pollutants and smoking to transfer factor for CO. The diffusion capacity is the technique that measures the ability of the respiratory system for gas exchange, thus allowing a diagnosis of the malfunction of the alveolar-capillary unit. The most important parameter to assess is the CO diffusion capacity (DLCO).

Limitation of air flow is usually progressive and followed by abnormal inflammatory responses of lungs to the action of particles and harmful gases, particularly to workplace emissions, but also in interaction with tobacco smoke. Inflammatory process related to COPD is characterised by growth of number of activated alveolar macrophages, neutrophils, CD8 + T cytotoxic lymphocytes, B lymphocytes, CD4 + T lymphocytes and with the release of numerous inflammatory mediators (leukotrienes, cytotoxins, growth factor, chemokine, oxidants and proteases). Chronic inflammation leads to a reconfiguration of minor airways with lumen obstruction because of increase of mucus production, and as a result of thickening of walls of breathing ways caused by oedema and by forming of collagen which causes fibrosis and narrowing of respiratory ways (12-13), (14-18), (19-23). Tobacco smoke also stimulates inflammatory reaction which includes some mechanisms, including activation of the complement, activation of alveolar macrophages and epithelial cells of respiratory ways which in an increased way release pro-inflammatory mediators. As a result of this exposure, it comes to blockage of regulatory mechanisms which enable the flow (mobility) and regulation of the inflammation (24).

Particular attention must be paid to the fact that differences at parameters of ventilation in lungs are quite small when comparing the groups. A significantly bigger difference was noticed in the measurements made to the transfer factor for CO. This difference in transfer factor of CO was particularly higher at smokers. The fact that the transfer factor has faced a significant decrease at the participants, especially at smokers indicates the changes that have occurred not only at the airways of respiratory tract, but also at terminal bronchioles, and also at the alveolar capillary membrane.

These changes are as a result and consequence of a permanent inflammatory reaction rather than as a direct result of toxic effects of coal dust at breathing trunk. The inflammation itself leads to oxidation, and later to accumulation of inflammatory cells, whereas at an advanced stage it leads to accumulation of connective tissue. It is common that accumulation of connective tissues is called remodelling. Remodelling is not a term which is exclusively related to the respiratory system, until the transfer factor experiences changes only in case of anomalies in the level of alveolar capillary membrane.

The only constant value which is permanently present is the presence of inflammation which comes as a result of effects of toxic substances. Presence of respiratory symptoms; cough, coughing, the feeling of chest wheezing, was significantly higher at the exposed groups compared to the control group. This fact shows that long term absorption of pollutants and coal dust causes changes in the tracheobronchial trunk, causing a known symptomatology.

The DLCO measurement is not substantially influenced by airway calibre. It is therefore an easy, non-invasive means of examining the integrity of the lung parenchyma in vivo and of monitoring the course of obstructive and restrictive lung diseases. Cross sectional studies have shown that asbestos exposure reduces DLCO (25-27), where was analysed the effects of crocidolite (blue asbestos) and tobacco smoking on changes in DLCO over time. As was find this is the first longitudinal study evaluating interactions between the effect of asbestos and smoking on gas diffusion. The proportion of asbestos exposed subjects with obstructive pulmonary impairment was about 2.5 times higher than that of the controls. Moreover, the FEV1/FVC ratio generally reflects large airways function, and the earliest asbestos lung lesions are peri-bronchiolar, and abnormalities in this anatomic region of the lung are not well-captured on standard pulmonary function testing (28).

CONCLUSIONS

Based on our research and comprehensive analyses and mutual relations of various direct and indirect pulmonary function we can determine that:

1. Analysis of the frequency of respiratory symptoms, differences in the function of lungs, bronchial hyper-responsiveness, changes in the balance of pressure of partial gases and changes in the transfer factor of CO at the participants from mining basins, who have been exposed to high air pollution concentrations, have indicated potential damages to the function of exchange of gases in lungs, the values of partial pressure in capillary blood for PaO_2 and $PaCO_2$ to exposed workers and control group workers we got significant statistical differences ($p<0.001$).

2. Based on the study of the respiratory function of lungs, we have come to conclusions that differences found for ventilation parameters are small and at a significant limit. Whereas significant differences have been found in the transfer factor of CO at workers of the group of category of smoking participants from Trepça ($p <0.05$), compared to other groups indicating the importance of interaction between smoking and harmful effects of contaminants in transfer of gases through alveolar membrane.

3. Results of the study have shown that frequency of respiratory symptoms - cough, coughing and chest wheezing – are considerably higher at almost all workers of all industrial plants, but in particular at lead and zinc smelter workers compared to control group workers. Differences were significant ($p = 0.0041$), when speaking about cough in general. Whereas the statistical analysis of suffocation attacks and wheezing and presence of productive cough (which is a characteristic of infectious bronchitis) did not show significant differences ($p = 0,141$).

4. This study undoubtedly indicates that exposure to workplace harmful agents such as sulphur dioxide, sulphur trioxide, carbon monoxide, sodium oxides, coal dust, soot and other pollutants. It is a consequence of increase of bronchial hyper-responsiveness and reduction of transfer factor of carbon monoxide which in reality shows a decrease of transfer factor, what in practice means deterioration and obstruction of flow of gases through the alveolar capillary membranes, which was significantly higher in the group of workers exposed to various pollutants, compared to the control group at a significant level ($p <0.001$).

5. This study also shows an important correlation between the duration of exposure and the harmful air pollutants and morbidity related to response of the respiratory system noticed through the presence of respiratory symptoms, differences at spirometric parameters, reduction of transfer factor and presence in a considerable manner of the general inflammatory syndrome.

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6. Our study shows the need for a continuous monitoring of macro and micro ecology to determine the level of concentration of pollutants as causes of diseases, appropriate and adequate reaction in case of increase of pollutants emission, for any reason it could happen.

Abbreviations

COPD - Chronic obstructive pulmonary disease
FEV1- Forced expiratory volume in one second
100 x FEV1/FVC - Tiffneau Index
FRC - functional residual capacity
TPC - total pulmonary capacity
RV - residual volume
FVC - Forced volume capacity
$FEF_{25\%}$, forced expiratory flow at 25% of FVC
$FEF_{50\%}$, forced expiratory flow at 50% of FVC
$FEF_{75\%}$, forced expiratory flow at 75% of FVC
$FEF_{25\%-75\%}$ forced expiratory flow between 25% and 75% of FVC

DLCO - Diffusing capacity of the lung for carbon monoxide
PaO_2 - partial pressure of oxygen
$PaCO_2$ - partial pressure of carbon dioxide
ITGV - intrathoracic gas volume
Raw (Rt) - airway resistance
DGVF's - dusts, noxious gases/vapors, and fumes
MRCQ – modified research council questionnaire on respiratory symptoms
SRT = Rt x ITGV - The specific resistance
ANOVA - Analysis of variance, statistical method.
INSTAT-3 - GraphPad InStat is a commercial scientific statistics software
X - the median value
SD - standard deviation
SEM - standard error

Declarations

Ethics approval

Informed consent to participate in the study was obtained from all participants after the purpose and methods were clearly explained; and participants were assured that they could withdraw from the study at any time without any consequences. The participants treated ethically and the Institute's ethics committee approved the content of our study protocol and granted ethical clearance. All data was collected in accordance with scientific standards specified by Faculty of Medicine 's Act on Research Involving Human Beings and in compliance with the national ethical guidelines on the handling of personal data in the field of medicine issued by the Medical Commission for Ethics reconfirmed with the protocol number No. 2417 of date 21.03. 2016.

Ethical Consideration on animals
Not applicable.

Consent for publication

Not applicable.

Competing interests

There are no financial or non-financial competing interests related to this manuscript.

Authors' contributions

BK coordinated the project and drafted the manuscript, worked on most of the writing, literature review, all illustrations and contributed to the design of this paper with the assistance of HI. AB contributed to the specific aspects related to existing data integration methodologies and key references. All network partners (PI, TK, KH) helped to draft the manuscript. MC, as responsible for administrative activities, gave a substantial contribution throughout the project. The staff of seventh persons was involved in the daily operations. All authors read and approved the final manuscript for submission.

Availability of data and material

The datasets analysed during the current study are available from the corresponding author on reasonable request. Complete documentation of this manuscript is stored in archives of Institute of Clinical Physiology –Faculty of Medicine of the University Hasan Prishtina Kosovo.

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